Brigham and Women's Hospital
Founding Member, Mass General Brigham

Recent Advances in Lipid Therapy and Cardiovascular Disease Risk Reduction

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DISCLOSURES

Grants
Allelica, Amgen, Apple, AstraZeneca, Boston Scientific, Cleerly, Novartis, Roche / Genentech, Silence Therapeutics

Consultant
AiRNA, Allelica, Amgen, Apple, AstraZeneca, Bain Capital, Blackstone Life Sciences, Bristol Myers Squibb, Creative Education Concepts, CRISPR Therapeutics, Eli Lilly & Co, Esperion Therapeutics, Foresite Capital, Foresite Labs, GV, HeartFlow, Incyte, Magnet Biomedicine, Merck, Novartis, Novo Nordisk, Roche / Genentech, TenSixteen Bio, Tourmaline Bio, Ursa Medicines

Equity
Bolt, Candela, Mercury, MyOme, Parameter Health, Preciseli, TenSixteen Bio

Royalties
Recora

Spousal Employment
Vertex Pharmaceuticals

OBJECTIVES

- Recognize the role of AHA PREVENT in initializing the CPR (Calculate, Personalize, Reclassify/Refine) framework.
- Understand the utility of lifetime risk estimation in risk optimization in younger individuals.
- Identify indications for and limitations of coronary artery calcium scoring.
- Recognize the roles of complementary biomarkers (lipoprotein(a), apolipoprotein B).
- Identify the breadth of lipid-lowering agents aimed at optimizing LDL cholesterol.

2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association

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CASE #1

A 36 yo man of South Asian ancestry presents for routine health maintenance. He has no personal history of cardiovascular disease, diabetes, or hypertension. He does not smoke. His father had a myocardial infarction at 58 yo.

BMI	**24.1 kg/m^2**
Blood pressure	**128/78 mmHg**
Total cholesterol	**258 mg/dl**
LDL-C	**172 mg/dl**
HDL-C	**47 mg/dl**
Triglycerides	**195 mg/dl**
eGFR	**96 mL/min/1.73m^2**

He is not on any medications. He asks about his cardiovascular risk and whether he needs a statin.

When applying the AHA PREVENT equation to guide statin decision-making in this patient, which of the following statements is most accurate?

A. The patient cannot be risk-stratified because PREVENT does not include patients < 40y of age.

B. His 10-year ASCVD risk by PREVENT is >10%, indicating that high-intensity statin is warranted.

C. PREVENT estimates his 10-year ASCVD risk as low (<3%), but his LDL-C of 172 mg/dl places him in a range where a statin is reasonable.

D. PREVENT estimates his 10-year ASCVD risk as low (<3%), so guidelines recommend against a statin.

E. PREVENT incorporates South Asian ancestry in its risk estimation.

CASE #1 - ANSWER

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AHA PREVENT CALCULATOR: IMPROVED CALIBRATION

Models	Total CVD		ASCVD	
	Female	Male	Female	Male
Pooled cohort equations*				
C-statistic (IQI)	0.789 (0.746 to 0.802)	0.747 (0.721 to 0.767)	0.772 (0.729 to 0.782)	0.733 (0.701 to 0.751)
C-statistic (95% CI)† of PREVENT minus pooled cohort equations	0.009 (0.008 to 0.011)	0.008 (0.007 to 0.009)	0.007 (0.006 to 0.009)	0.005 (0.004 to 0.006)
Calibration slope (IQI)	0.84 (0.65 to 1.00)	0.67 (0.60 to 0.81)	0.54 (0.47 to 0.61)	0.50 (0.39 to 0.52)
PREVENT model enhanced for all novel predictors§				
No. of cohorts	18	18	18	18
No. of participants	606 662	468 195	606 662	468 195
No. of events	15 059	14 084	9423	9456
Base model C-statistic (IQI)	0.807 (0.787 to 0.816)	0.774 (0.751 to 0.788)	0.793 (0.761 to 0.800)	0.752 (0.737 to 0.772)
Base model enhanced for all novel predictors C-statistic (IQI)	0.813 (0.794 to 0.820)	0.776 (0.762 to 0.793)	0.799 (0.767 to 0.804)	0.755 (0.742 to 0.776)
ΔC-statistic (95% CI)†	0.004 (0.004 to 0.005)	0.005 (0.004 to 0.007)	0.004 (0.003 to 0.005)	0.004 (0.002 to 0.006)
NRI (IQI)	0.005 (–0.000 to 0.018)	0.006 (0.000 to 0.021)	0.009 (0.001 to 0.023)	0.008 (–0.009 to 0.015)
Calibration slope (IQI)	1.05 (0.73 to 1.20)	0.95 (0.72 to 1.10)	1.11 (0.96 to 1.41)	1.01 (0.83 to 1.18)

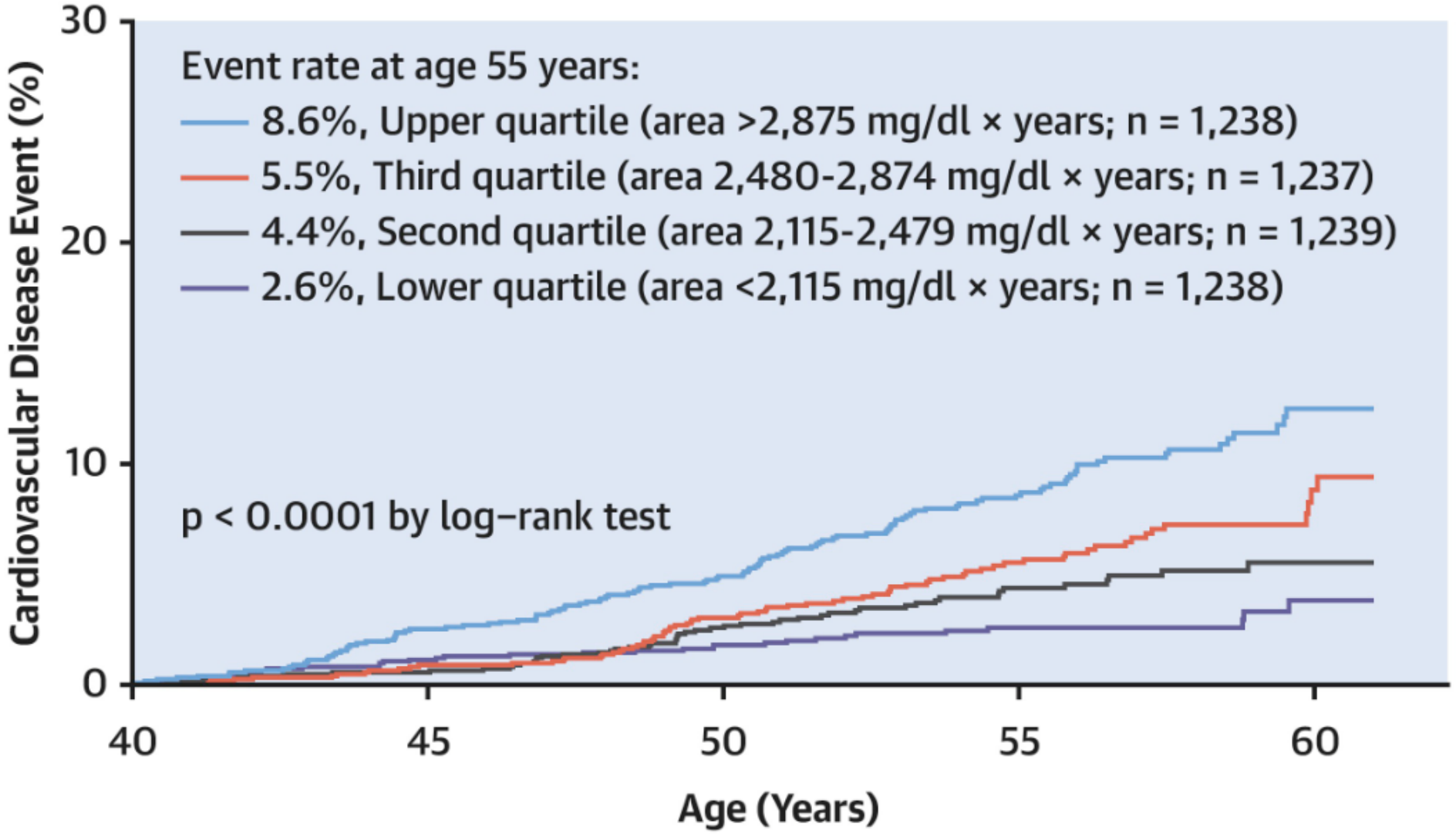
CONSIDER STATINS EARLIER TO ADDRESS HIGH LIFETIME RISK

Table 12. Crosswalk Between 10-Year Risk ASCVD Estimates From PCE and PREVENT-ASCVD Equations

	Approximate Equivalent Ranges of 10-Year ASCVD Risk Estimates*	
Risk Group	**PCE**	**PREVENT-ASCVD**
Low	<5%	<3%
Borderline	5% to <7.5%	3% to <5%
Intermediate	7.5% to <20%	5% to <10%
High	≥20%	≥10%

Low (<3%) Estimated 10-Year ASCVD Risk		
1	A	2. In adults aged 30 to 59 y, at low (<3%) 10-y estimated risk for ASCVD who have an LDL-C <160 mg/dL (4.1 mmol/L) and a 30-y risk estimate of <10%, counseling on health behaviors is recommended to reduce LDL-C and risk for ASCVD.[1–4]
2a	C-LD	3. In adults aged 30 to 59 y, at low (<3%) 10-y estimated risk for ASCVD but with an LDL-C of 160 to 189 mg/dL (4.1–4.9 mmol/L) or a 30-y ASCVD risk ≥10% (for those aged 30–59 y), a moderate-intensity statin is reasonable to reduce cumulative exposure to atherogenic lipoproteins.[5,6]

CUMULATIVE LDL-C AND INCIDENT ASCVD RISK



CASE #2

A 44 yo woman presents for a new patient preventive care visit. She has no personal history history of cardiovascular disease, diabetes, or hypertension. She does not smoke and has no family history of premature ASCVD. She takes no medications.

Her first pregnancy at 28 yo was complicated by gestational diabetes, managed with diet alone, and resulted in a term delivery. Her second pregnancy at age 31 yo was complicated by preeclampsia without severe features, delivering at 39 weeks. Her third pregnancy at age 35 yo was uncomplicated. She has had regular menstrual cycles and has not yet entered menopause.

BMI	**25.8 kg/m^2**
Blood pressure	**122/74 mmHg**
Total cholesterol	**222 mg/dl**
LDL-C	**144 mg/dl**
HDL-C	**58 mg/dl**
Triglycerides	**102 mg/dl**
HbA1c	**5.4%**
Lp(a)	**38 nmol/L**
eGFR	**92 mL/min/1.73m^2**

Her 10-year PREVENT-ASCVD is calculated at 0.8%. Which of the following best describes the role of her obstetric history in ASCVD risk assessment and statin decision-making?

CASE #2

A. Both gestational diabetes and preeclampsia are recognized risk-enhancing factors, together supporting statin therapy initiation after clinician-patient discussion.

B. Gestational diabetes is a recognized risk-enhancing factor, but preeclampsia without severe features is not a risk-enhancing factor.

C. While both gestational diabetes and preeclampsia are recognized risk-enhancing factors, with a low 10-year ASCVD risk by PREVENT, guidelines support lifestyle counseling and reassessment rather than statin initiation.

D. Reproductive risk markers such as gestational diabetes and preeclampsia reflect pregnancy-specific pathophysiology that resolve postpartum and not impact future cardiovascular risk.

E. Because her current HbA1c is normal, her history of gestational diabetes is not relevant to her cardiovascular risk assessment.

CASE #2 - ANSWER

A. Both gestational diabetes and preeclampsia are recognized risk-enhancing factors, together supporting statin therapy initiation after clinician-patient discussion.

B. Gestational diabetes is a recognized risk-enhancing factor, but preeclampsia without severe features is not a risk-enhancing factor.

C. While both gestational diabetes and preeclampsia are recognized risk-enhancing factors, with a low 10-year ASCVD risk by PREVENT, guidelines support lifestyle counseling and reassessment rather than statin initiation.

D. Reproductive risk markers such as gestational diabetes and preeclampsia reflect pregnancy-specific pathophysiology that resolve postpartum and not impact future cardiovascular risk.

E. Because her current HbA1c is normal, her history of gestational diabetes is not relevant to her cardiovascular risk assessment.

RISK ENHANCERS

COR	LOE	Recommendations
2a	B-NR	1. In adults without ASCVD with a borderline 10-y ASCVD risk estimate (3% to <5%) by the PREVENT-ASCVD equations, consideration of risk enhancers is reasonable to personalize risk assessment and the potential benefit of initiating LLT as an adjunct to lifestyle management to reduce ASCVD risk (Table 13).[1–18]

Table 13. Risk Enhancers

Risk Enhancers
History of premature ASCVD in a parent or sibling (onset age <55 y for men, <65 y for women)
Higher risk ancestry (eg, South Asian, Filipino)
High polygenic risk (if measured) (Section 4.2.3.5, "Polygenic Risk Scores")
Chronic inflammatory diseases (eg, systemic lupus, rheumatoid arthritis, advanced psoriasis, inflammatory arthritis)
Lp(a) ≥125 nmol/L or ≥50 mg/dL
hsCRP ≥2 mg/L on >1 occasion (if measured)
TG persistently ≥175 mg/dL (2 mmol/L) (if nonfasting) and ≥150 mg/dL (1.7 mmol/L) (if fasting)
CKM syndrome
LDL-C persistently ≥160–189 mg/dL (4.1–4.9 mmol/L), non–HDL-C ≥190–219 mg/dL or apoB ≥120 mg/dL*
Reproductive risk markers (premature menopause, preeclampsia, gestational diabetes, gestational hypertension, preterm delivery; Section 4.2.3.4, "Reproductive Risk Marker")

INDEPENDENT RISKS LINKED TO HYPERTENSION AND DIABETES DURING PREGNANCY

Table 2. Event Rates and Hazard Ratios for the Association of Gestational Hypertensive Disorder and Gestational Diabetes With Incident Cardiovascular Disease

	Early phase (initial 5 years after index pregnancy)					Late phase (after the initial 5 years following the index delivery)				
		Hazard ratio (95% CI)					Hazard ratio (95% CI)			
Exposures	Crude IR per 10 000 PY (95% CI)	Unadjusted	Adjusted model 1[a]	Adjusted model 2[b]	Adjusted model 3[c]	Crude IR per 10 000 PY (95% CI)	Unadjusted	Adjusted Model 1[a]	Adjusted Model 2[b]	Adjusted Model 3[c]
No GHTD and no GD	1.94 (1.80-2.08)	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	3.54 (3.32-3.78)	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Isolated GD	1.89 (1.42-2.52)	0.99 (0.75-1.31)	0.84 (0.63-1.12)	0.82 (0.61-1.09)	0.80 (0.60-1.06)	6.05 (4.95-7.39)	1.76 (1.42-2.18)	1.50 (1.21-1.87)	1.44 (1.151-1.79)	1.19 (0.95-1.50)
Isolated GTHD	4.04 (3.25-5.02)	2.33 (1.89-2.87)	2.40 (1.95-2.96)	2.13 (1.72-2.63)	1.90 (1.53-2.35)	8.18 (6.78-9.86)	2.10 (1.69-2.60)	2.19 (1.76-2.72)-	1.90 (1.53-2.38)	1.41 (1.12-1.76)
GHTD and GD	4.47 (2.41-8.31)	2.32 (1.28-4.21)	2.04 (1.12-3.70)	1.71 (0.94-3.10)	1.42 (0.78-2.58)	18.89 (12.86-27.74)	5.61 (3.77-8.35)	4.99 (3.34-7.42)	4.05 (2.71-6.05)	2.43 (1.60-3.67)

Abbreviations: GD, gestational diabetes; GHTD, gestational hypertensive disorder; IR, incidence rate; PY, person-years.

[a] Model 1: adjusted for age, neighborhood income quintile, and parity.

[b] Model 2: model 1 plus rurality, chronic kidney disease, prior gestational hypertensive disorder, and prior gestational diabetes.

[c] Model 3: model 1 plus postpartum diabetes and postpartum hypertension.

INCORPORATE REPRODUCTIVE RISK MARKERS

COR	LOE	Recommendation
2a	B-NR	1. In adults without ASCVD, consideration of reproductive risk markers, such as early menopause (<45 y) and history of adverse pregnancy outcomes (gestational hypertension, preeclampsia, gestational diabetes, preterm delivery) is reasonable to personalize ASCVD risk assessment when considering the potential benefit of initiating LLT as an adjunct to lifestyle management for primary ASCVD prevention.[1–5]

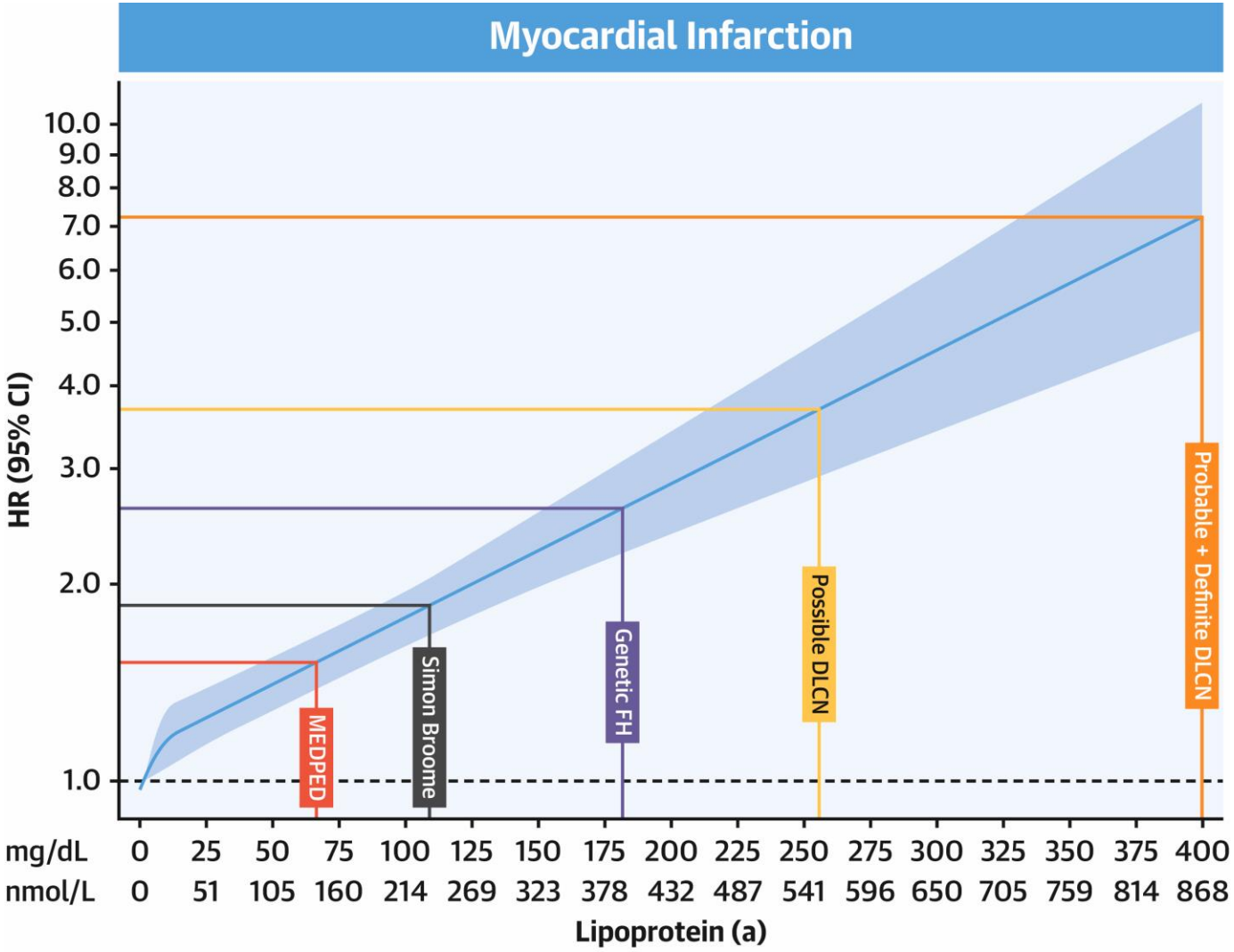
Table 14. Reproductive Risk Markers Associated With ASCVD Events

Adverse Pregnancy Outcomes* That Have a Stronger Association With ASCVD Events[14]
Hypertensive disorders of pregnancy (preeclampsia, gestational hypertension)
Gestational diabetes
Small-for-gestational age[23] (birthweight below the 10th percentile[24])
Preterm delivery (before 37 wk gestation)
Recurrent spontaneous pregnancy loss
Other Reproductive Risk Markers[11]
Early menarche (<10 y old)[25]
Early menopause (<45 y old),[18] especially premature menopause (<40 y old)[18,21]
Polycystic ovarian syndrome and irregular menses[26,27]

LIPOPROTEIN(a) MEASUREMENT

1	B-NR	1. In all adults, measurement of Lp(a) concentration is recommended at least once for ASCVD risk assessment.[1–4]

LIPOPROTEIN(a): ORTHOGONAL RISK AXIS



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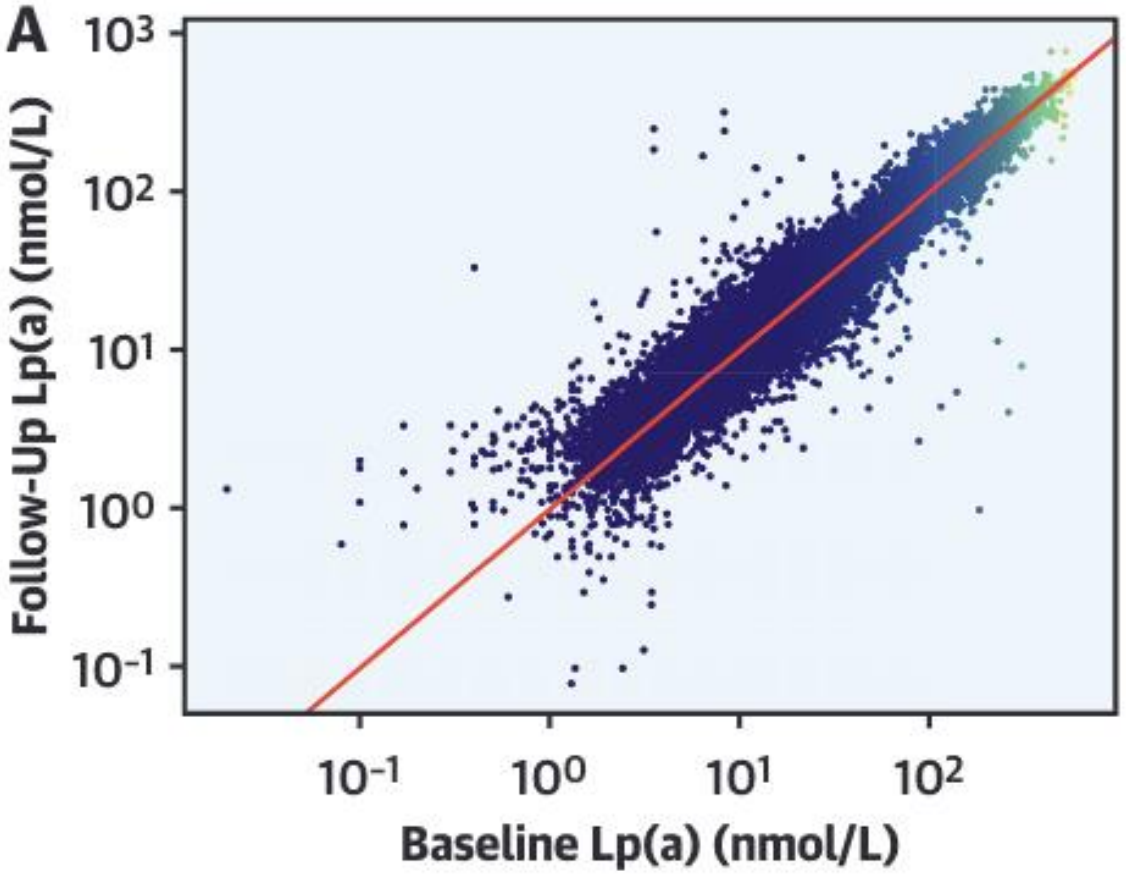
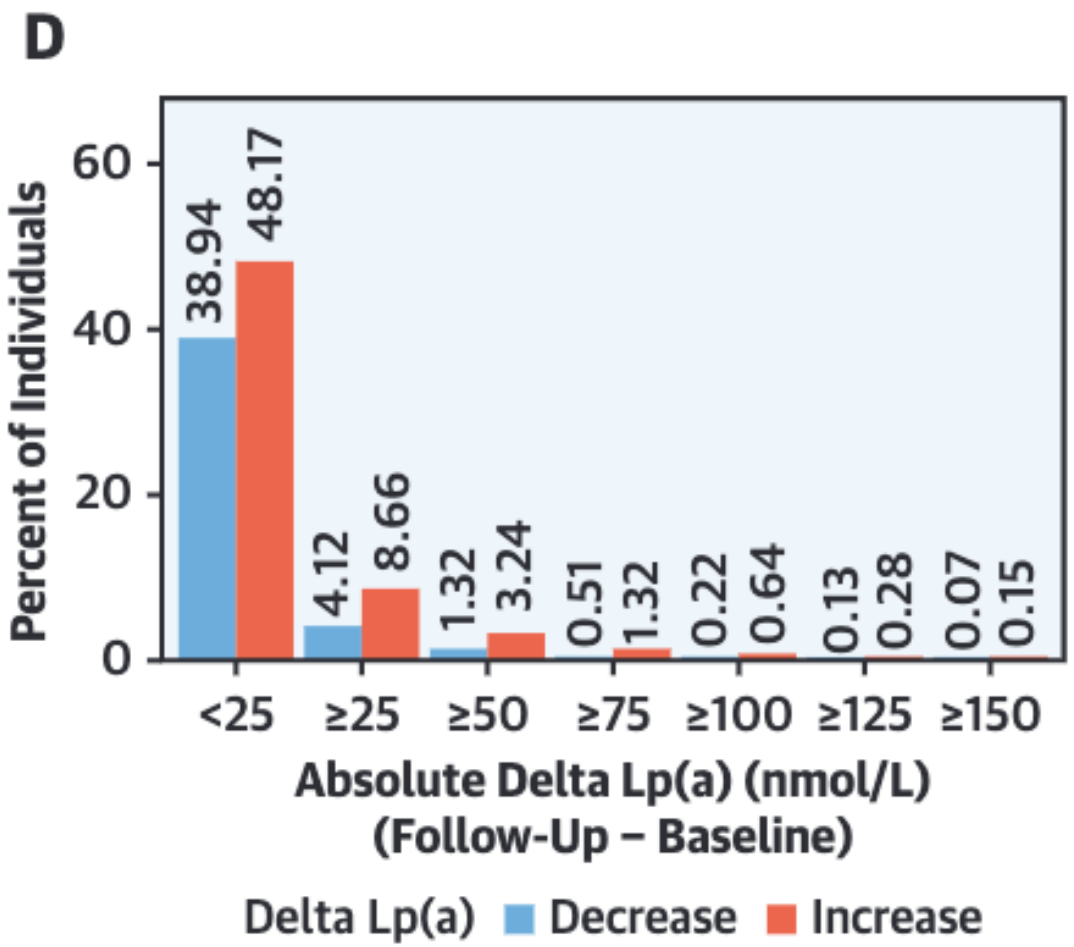
GENERALLY, DO NOT NEED TO REPEAT LIPOPROTEIN(a) MEASUREMENT





Trinder M et al *JACC* 2022

CASE #3

A 54 yo man presents for a follow-up visit. He has no personal history of cardiovascular disease, diabetes, or smoking. He has hypertension and is prescribed lisinopril 10mg daily. His father had a myocardial infarction at age 65 years.
Eight weeks ago, his 10-year PREVENT-ASCVD risk was calculated at 5.8%. After discussing potential benefits and uncertainties of statin therapy, he remain decided. CAC scoring was obtained to resolve the therapeutic uncertainty. His CAC score was 95 AU, at the 81st percentile for age, sex, race/ethnicity.

BMI	**29.8 kg/m^2**
Blood pressure	**136/78 mmHg**
Total cholesterol	**235 mg/dl**
LDL-C	**155 mg/dl**
HDL-C	**40 mg/dl**
Triglycerides	**201 mg/dl**
HbA1c	**5.8%**
Lp(a)	**27 nmol/L**
eGFR	**88 mL/min/1.73m^2**

What is the most appropriate lipid-lowering strategy?

CASE #3

A. Start moderate-intensity statin, with goal 30-49% LDL-C-lowering and LDL-C <100 mg/dl.

B. Start a high-intensity statin, with goal >50% LDL-C-lowering and LDL-C <70 mg/dl.

C. Defer statin therapy since CAC score is <100 AU.

D. Obtain a repeat CAC in 3-5 years since progression data is needed to determine the appropriate statin intensity.

E. Start evolocumab 140mg sc q2w, with goal >50% LDL-C-lowering and LDL-C <55 mg/dl.

CASE #3 - ANSWER

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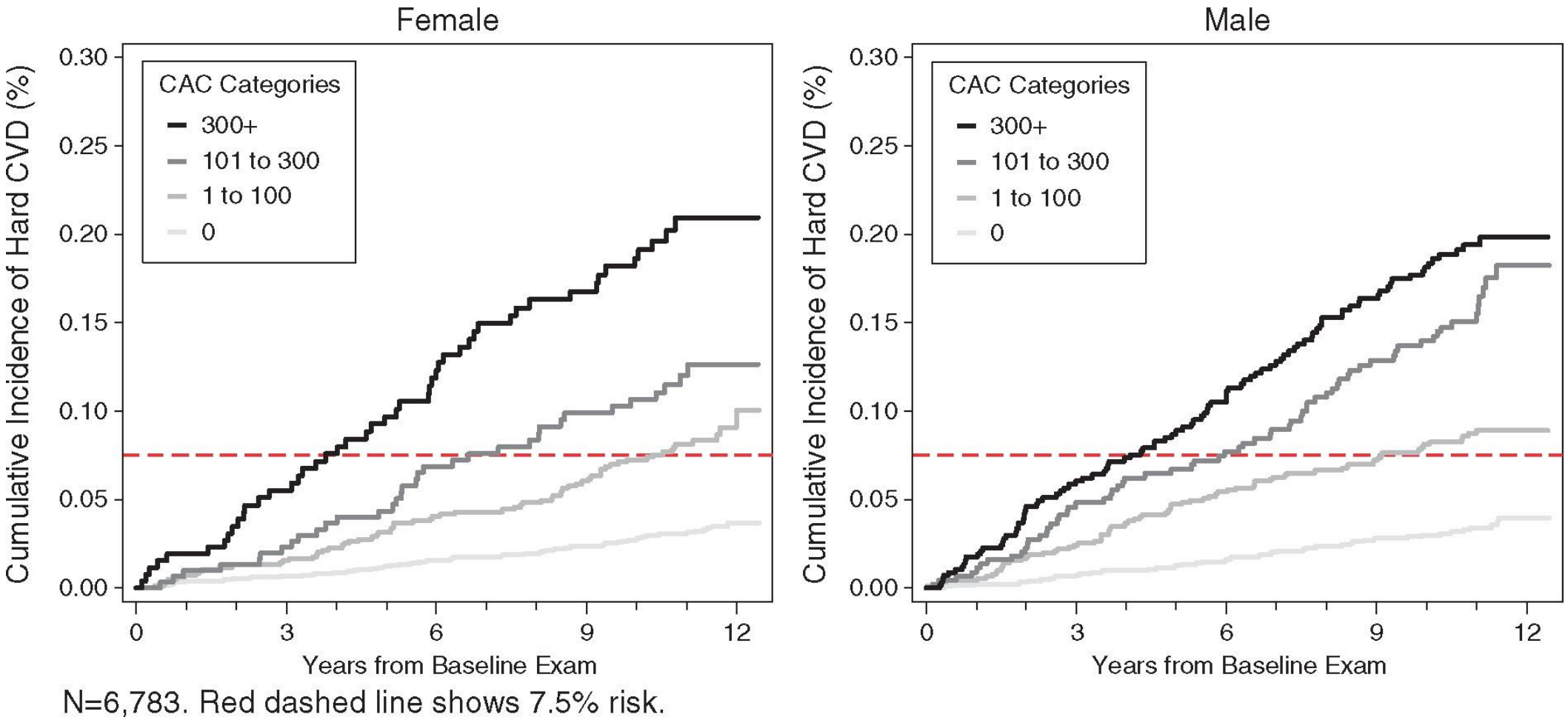
10-YEAR ASCVD RISK BY CAC IN MESA



N=6,783. Red dashed line shows 7.5% risk.

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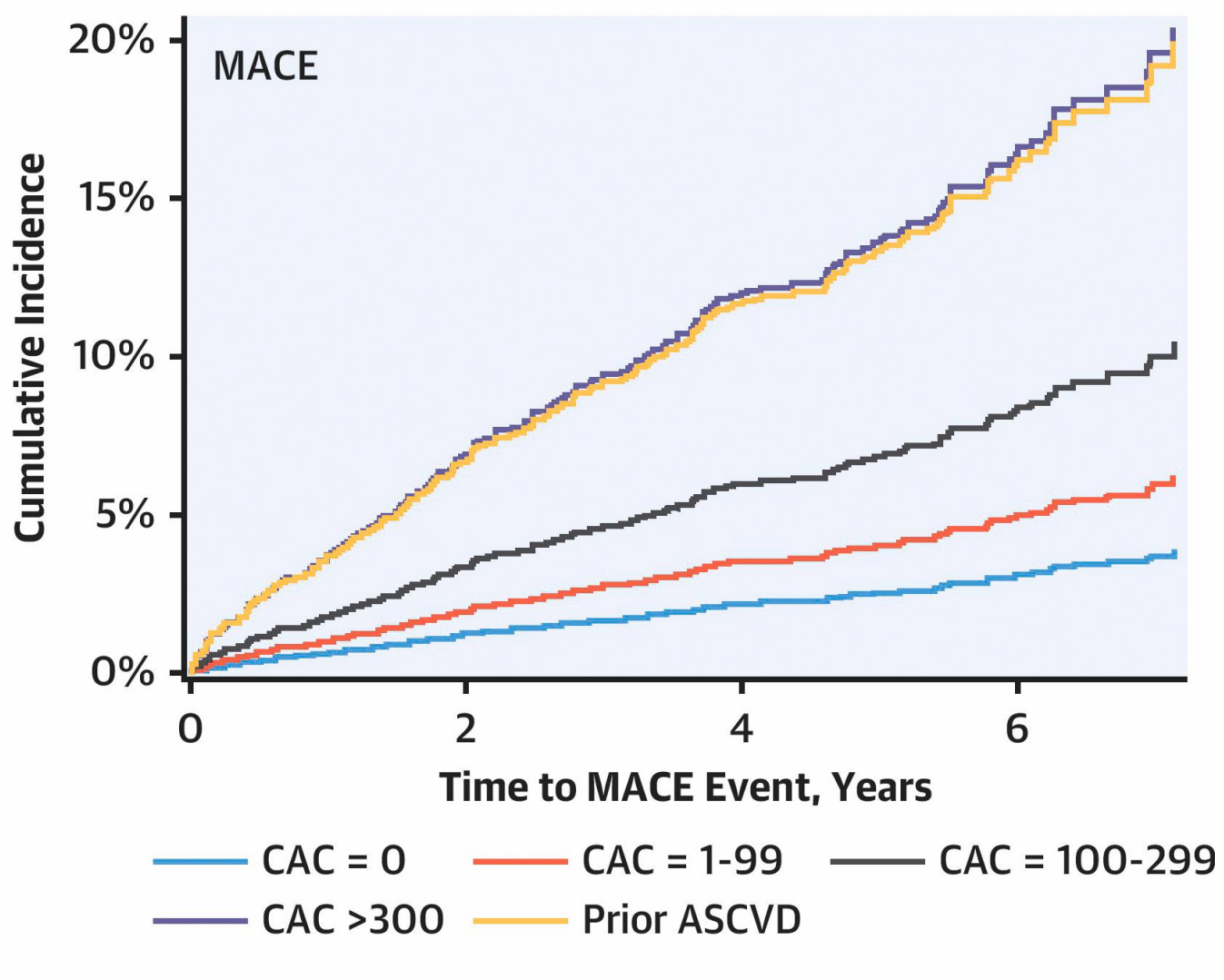
CAC 300 ~ SECONDARY PREVENTION



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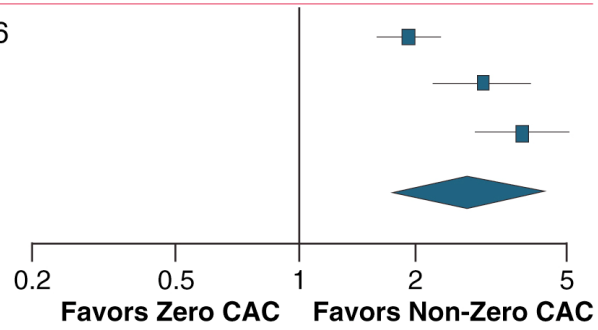
PRESENCE OF CAC PREDICTS STATIN ADHERENCE

Lipid Lowering Medication Initiation

Study	Nonzero Events	CAC Total	Zero Events	CAC Total	Weight	Odds Ratio M-H, Random, 95% CI	Follow-up Years
Nasir et al., 2010	317	2295	200	2669	35.2%	1.98 [1.64, 2.38]	1.6
Rozanski et al., 2011	190	458	94	505	32.2%	3.10 [2.32, 4.15]	4
Taylor et al., 2008	121	321	162	1215	32.6%	3.93 [2.97, 5.20]	6
Total (95% CI)	**628**	**3074**	**456**	**4389**	**100.0%**	**2.86 [1.85, 4.41]**	

Test for overall effect: Z = 4.74 (P < 0.0001)

Heterogeneity: Chi^2 = 18.07, df = 2 (P = 0.0001); I^2 = 89%

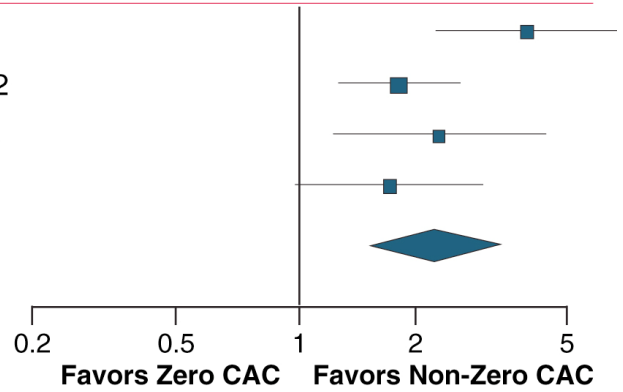


Lipid Lowering Medication Continuation

Study	Nonzero Events	CAC Total	Zero Events	CAC Total	Weight	Odds Ratio M-H, Random, 95% CI	Follow-up Years
Kalia et al., 2006	332	441	28	64	24.1%	3.92 [2.28, 6.71]	3
Nasir et al., 2010	553	803	77	140	33.1%	1.81 [1.26, 2.61]	3.2
Rozanski et al., 2011	185	205	96	120	19.9%	2.31 [1.22, 4.40]	4
Taylor et al., 2008	136	157	174	220	23.0%	1.71 [0.98, 3.01]	6
Total (95% CI)	**1206**	**1606**	**375**	**544**	**100.0%**	**2.26 [1.56, 3.28]**	

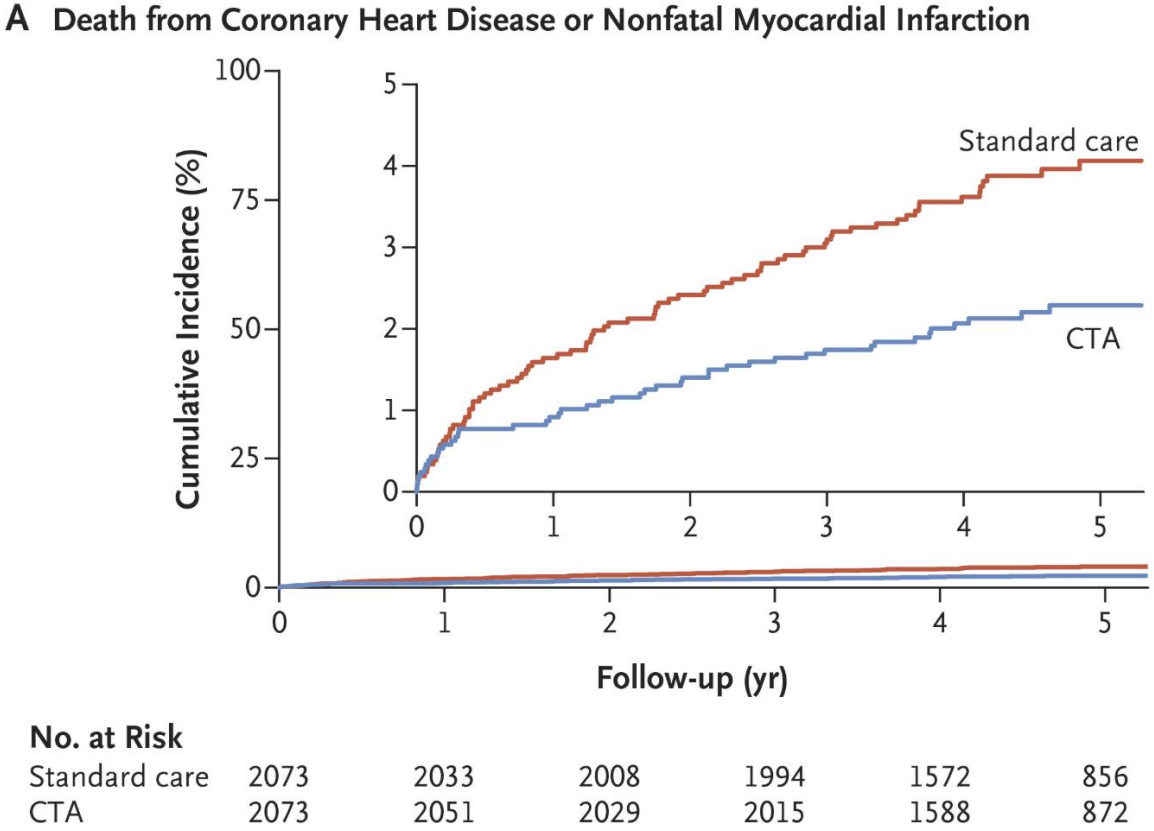
Test for overall effect: Z = 4.29 (P < 0.0001)

Heterogeneity: Chi^2 = 6.28, df = 3 (P = 0.1); I^2 = 52%



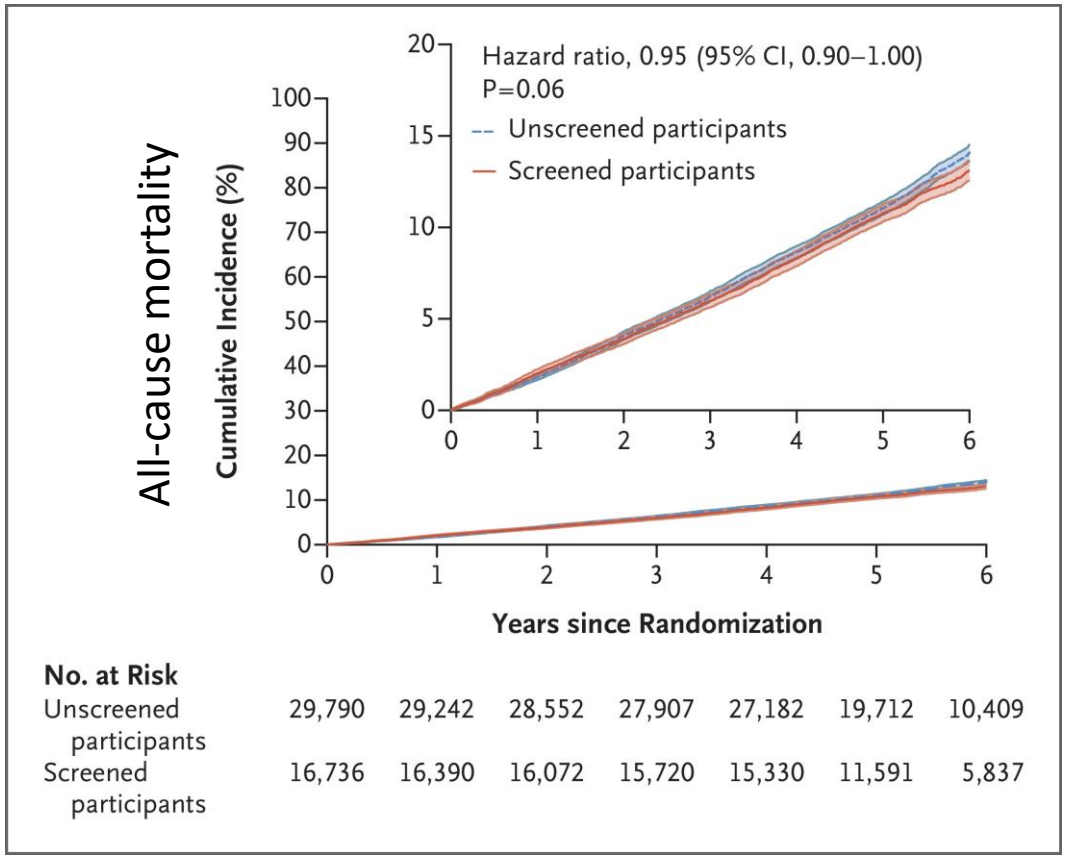
SCOT-HEART, DANCANVAS

Stable chest pain: CCTA + standard of care vs standard of care alone



SCOT-HEART

65-74yo Asymptomatic men: screening (CAC, ABI, lipids, HbA1c) vs control



DANCANVAS

ELEVATED ROLE FOR CAC

- Resolve treatment uncertainty for intermediate and select borderline risk (IIa -> I)
- Use presence of incidental CAC on non-gated CTs for influence LLT decisions (new, I)

Cardiac CT	Non-Cardiac CT	LDL-C Target
>1000		< 55 mg/dl (I)
300-999		< 70 mg/dl (I), <55 mg/dl (IIa)
100-299, or >75th percentile	Moderate-to-severe	< 70 mg/dl (I)
1-99 and <75th percentile	Mild	< 100 mg/dl (IIa)

CASE #4

A 67 year-old man with a history of anterior ST elevation myocardial infarction 2 years ago, treated with primary PCI and drug-eluting stent placement, presents for follow-up. He has type 2 diabetes on metformin and empagliflozin, and hypertension on amlodipine. He does not smoke. He also has a history of gout and prostate cancer in remission.

He has been on rosuvastatin 40mg daily since his event, and evolocumab 140mg sc every 2 weeks was added 6 months ago because of suboptimal LDL-C. Today's labs are his first follow-up since starting evolocumab.

BMI	**31.2 kg/m^2**
Blood pressure	**122/74 mmHg**
Total cholesterol	**134 mg/dl**
LDL-C	**48 mg/dl**
HDL-C	**38 mg/dl**
Triglycerides	**241 mg/dl**
HbA1c	**7.1%**
Lp(a)	**54 nmol/L**

What is the most appropriate lipid-lowering strategy?

CASE #4

A. Check apolipoprotein B.

B. Add fenofibrate.

C. Add ezetimibe.

D. Add bempedoic acid.

E. Switch evolocumab to inclisiran.

CASE #4 - ANSWER

A. Check apolipoprotein B.

B. Add fenofibrate.

C. Add ezetimibe.

D. Add bempedoic acid.

E. Switch evolocumab to inclisiran.

VERY HIGH RISK ASCVD

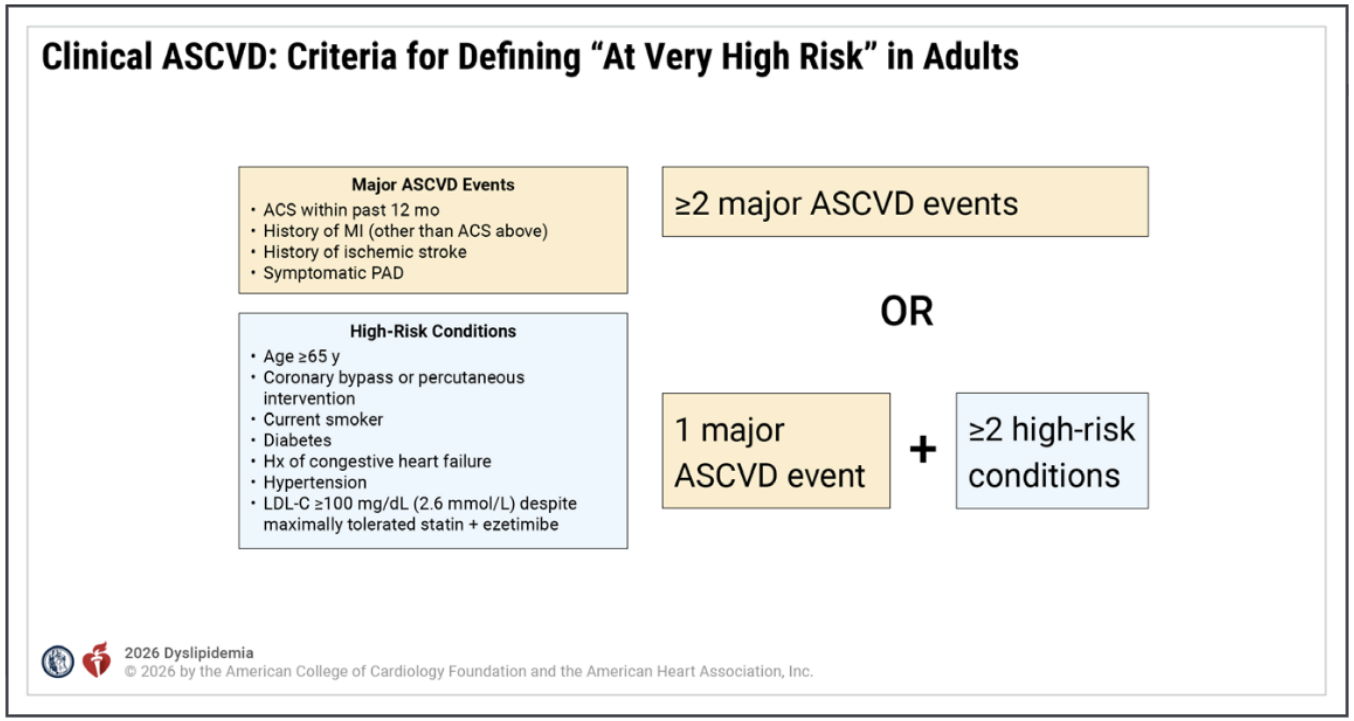
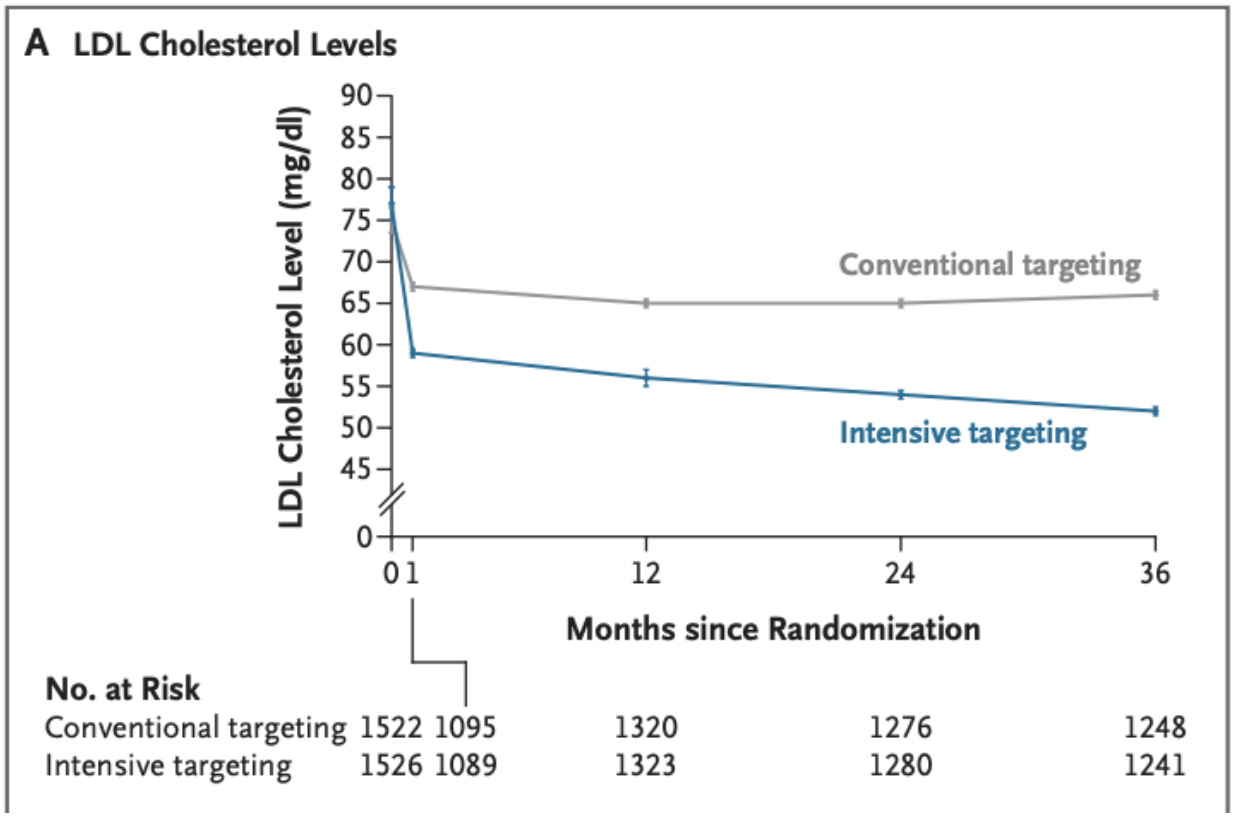
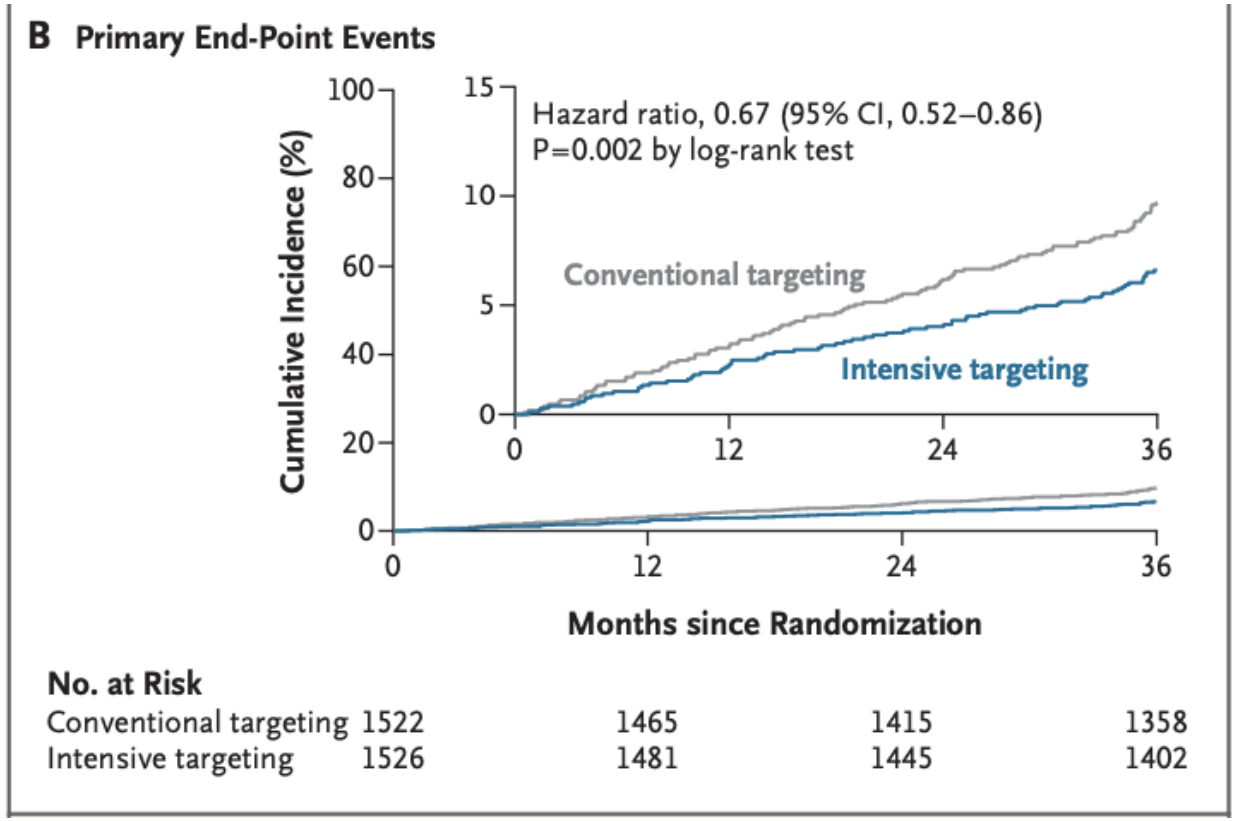


Figure 10. Clinical ASCVD: Criteria for Defining "At Very High Risk" in Adults.
ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; Hx, history; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and PAD, peripheral artery disease. Adapted with permission from Grundy et al.[13] © 2018 American Heart Association, Inc. and American College of Cardiology Foundation.

Criteria	LDL-C Target
Not Very High Risk	< 70 mg/dl (I), < 55 mg/dl (IIa)
Very High Risk	< 55 mg/dl (I)

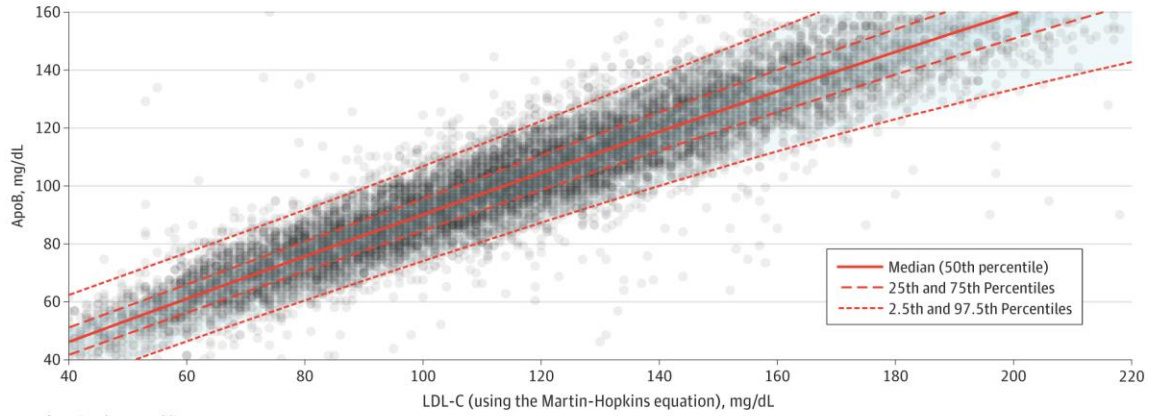
Ez-PAVE: LOWER IS BETTER





APOB IN NHANES

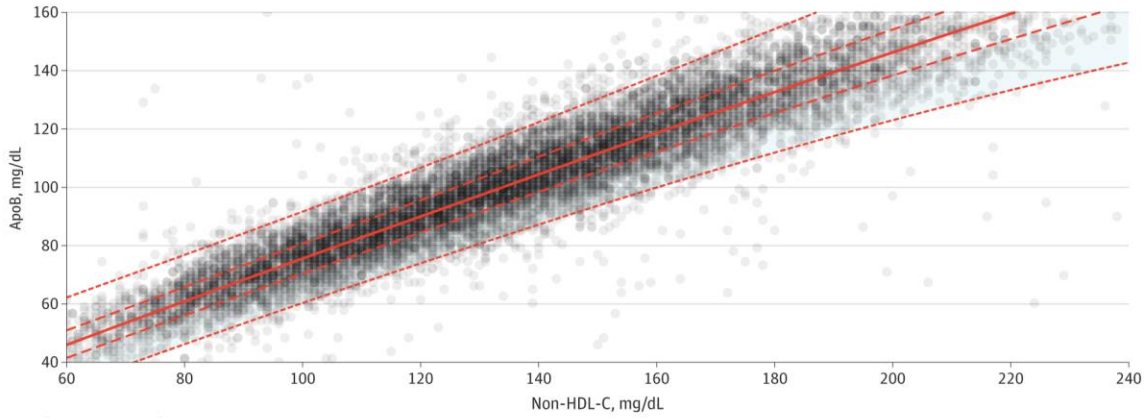
A Variation in apoB by LDL-C level



Potential range of apoB values, mg/dL

Measured LDL-C, mg/dL	55	70	100	130	160	190
2.5th Percentile	38	47	66	84	102	117
25th Percentile	45	56	75	95	114	132
50th Percentile	49	60	80	101	121	140
75th Percentile	54	64	86	107	128	149
97.5th Percentile	65	77	99	122	145	167

B Variation in apoB by non-HDL-C level



Potential range of apoB values, mg/dL

Measured non-HDL-C, mg/dL	85	100	130	160	190	220
2.5th Percentile	47	56	73	89	105	117
25th Percentile	56	64	82	100	116	132
50th Percentile	60	69	87	105	123	140
75th Percentile	64	73	92	111	129	147
97.5th Percentile	72	82	102	122	142	162

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APOB MEASUREMENT

COR	LOE	Recommendations
2a	B-NR	1. In adults on LLT, particularly those with ASCVD, CKM syndrome, type 2 diabetes, and/or elevated TG, measurement of apoB is reasonable to guide decisions regarding further therapeutic intensification once LDL-C and/or non–HDL-C goals are achieved.[1–8]

LDL-C Target	Non-HDL-C Target	ApoB Target
< 100 mg/dl	< 130 mg/dl	< 90 mg/dl
< 70 mg/dl	< 100 mg/dl	< 70 mg/dl
< 55 mg/dl	< 85 mg/dl	< 55 mg/dl

SUMMARY

- **Calculate**: Use AHA PREVENT for 10-year and, for selected patients, 30-year ASCVD risk estimation.
- **Personalize**: For borderline risk (3-5%), consider utilizing risk enhancers to better adjudicate likelihood of statin benefit.
- **Refine/Reclassify**: For intermediate risk (5-10%) when a statin decision remains uncertain, use CAC scoring to resolve. Also, if CAC information incidentally available from non-ECG gated CTs, consider this information.

- LDL-C targets: primary prevention <100 mg/dl, high risk primary prevention <70 mg/dl, secondary prevention <70 mg/dl, very high risk secondary prevention <55 mg/dl
  - If CAC available, titrate LDL-C target accordingly: 1-99 and <75th percentile <100 mg/dl, 100-299 or >75th percentile <70 mg/dl, 300-999 <70 mg/dl or <55 mg/dl, >1000 <55 mg/dl

- Consider verifying suitable lowering of atherogenic lipoproteins with apoB

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